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[FLUROXYPYR METHYLHEPTYL ESTER] PRENATAL DEVELOPMENTAL TOXICITY STUDY - RAT OPPTS 870.3700 [§83-3(a)]

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DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Study [rat] [§83-3 (a)]

DP BARCODE: D232217 SUBMISSION CODE: S515138
P.C. CODE: 128959 ID #: 062719-EIL STARANE F
REGISTRATION CASE NO.: 060640 CASWELL NO.: 463 O
TEST MATERIAL (PURITY): Fluroxypyr methylheptyl ester

SYNONYMS: ((4-amino-3,5-dichloro-6-fluoro-2-pyridinyl)oxy)acetic acid 1-methylheptyl ester; Fluroxypyr MHE, DOWCO*433 Ester

CITATION: Schroeder, R.E. (1994). A Developmental Toxicity Study in Rats with Fluroxypyr Methylheptyl Ester. Pharmaco LSR, Inc., Toxicology Services North America, NJ. Laboratory Project Study ID 93-4052, May 3, 1994. MRID 44094901. Unpublished.

SPONSOR: DowElanco

EXECUTIVE SUMMARY: Under the conditions of this developmental toxicity study [MRID 44094901], the administration of Fluroxypyr methylheptyl ester [95.8% a.i.] to 28 naturally-mated female Sprague-Dawley CD® [SD] BR rats/group via gavage at dose levels of 0 [Mazola® corn oil], 100, 300, and 600 mg/kg/day from days 6 through 15 of gestation resulted 8 deaths [following 4, 6, 7, 7, 8, 8, 10, 10 days of dosing] at the high-dose level and decreased body-weight gain [77% of control] and food consumption during the dosing period at this dose level also. Clinical signs observed in those dying on test included staining of the skin/fur in the ano-genital area, lethargy, hypothermia, labored breathing, irregular gait, pale appearance]. Excessive salivation was observed only in the treated dams, and although the incidence increased with dose, it is not clear whether this is a direct systemic effect of the test material or due to residual amounts of the test material in the buccal cavity from the dosing procedure. There were no treatment-related effects on gross pathologic alterations or absolute and relative liver and kidney weights at any dose level. Comparable pregnancy rates were observed among the groups, and there were no abortions, premature deliveries, or dams with 100% intrauterine deaths [except one mid-dose dam]. All dams had live fetuses at necropsy, and there were comparable numbers of corpora lutea, implantations, resorptions, and live fetuses among the groups. There were no dead fetuses. Fetal body weights and sex ratio were comparable among the groups, and there were no external malformations, visceral malformations or variations, or skeletal malformations that could be attributed to treatment. The overall incidences of fetuses and litters with fetuses with one or more ossification variation was comparable among the groups, but there was an increase in the incidences of incompletely ossified cervical vertebral transverse processes [mid- and high-dose levels, not dose-related] and incompletely ossified pubes at the high-dose level compared to the concurrent and historical controls. These increases occurred at a dose level that resulted in severe maternal toxicity [death].

The maternal NOEL is 300 mg/kg/day, the LOEL is 600 mg/kg/day, based on deaths and decreased body-weight gain and food consumption. The developmental toxicity NOEL is 300 mg/kg/day, and the LOEL is 600 mg/kg/day, based on an increase in incompletely ossified pubes].

This guideline [§83-3(a)] prenatal developmental toxicity study in the rat is classified Acceptable.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Fluroxypyr methylheptyl ester; Fluroxypyr MHE
Description: dark green to black solid
Batch #: Lot # EXTV 275-31 (AGR 283750)
Source: The Dow Chemical Company, Midland, Michigan
Purity: 95.8% a.i.
CAS #: 081404-37-3
[Structure]

2. Vehicle: Mazola® corn oil
Description: viscous yellow liquid
Lot/Batch #: Dec 03 93B
Source: Best Foods, CPC International, Inc.

3. Test animals: Strain: rat [outbred, albino]
Strain: CD® (Sprague-Dawley derived); (CD® [SD] BR)
Age: ♂♂ 49 days old [proven breeders, in-house colony]; ♀♀ 57 days old [date of receipt]; ♀♀ at mating 67 days
Weight: ♀♀ on day 0 of gestation 186-255 g
Source: Charles River Breeding Laboratories, Inc., Portage, Michigan
Housing: individual, except during mating
Diet: Purina Certified Rodent Chow® No. 5002 [mash], ad libitum.
Water: ad libitum
Environmental conditions: normal laboratory conditions
Acclimation period (P): 10 days [females]

B. PROCEDURES AND STUDY DESIGN

1. In-life dates - start: mating occurred on 10 nights as follows: June 3-4/7-11/15-17, 1993; June 10, 1993 [initiating of dosing]; end: July 8, 1993 [latest date on necropsy sheets]; May 3, 1994 [Study Director signed final report]

2. Mating: Selected females were naturally mated with one male nightly, and vaginal smears were taken early in the morning following intervals of nightly cohabitation; females were considered to have mated if sperm was noted microscopically in the vaginal rinse and/or a plug was observed in the vagina [day defined as day 0 of gestation]. The schedule for co-habitation allowed for the sacrifice of females at day 20 of gestation to occur during the work week and only 24 females were sorted per day. If more than 24 females mated at one time, the females excluded from the sorting procedure were determined using a random numbers table and the female's temporary cage card number.

3. Animal assignment: Mated females were assigned to the groups daily in such a way as to provide an equal distribution of mated females among groups and equalize, as far as possible, the day 0 gestation mean group body weights.

4. Dose selection rationale: The range-finding study, which included the use of the limit dose [1000 mg/kg/day], was used to select the dose levels for this definitive developmental toxicity study. Fluroxypyr methylheptyl ester was found to be toxic to the dams at dose levels of 750 and 1000 mg/kg/day [maternal deaths].

5. Dosage preparation and analysis

The test material, Fluroxypyr MHE, was administered as a suspension in Mazola® corn oil, such that a dose volume of 5 mL/kg body weight yielded the targeted dose. Appropriate amounts of test material were suspended in the vehicle. Two batches of each concentration were prepared [Batch # 1 prepared on June 7, 1993 and used June 10-22, 1993; Batch # 2 prepared on June 21, 1993 and used June 23-July 3, 1993] and stored at room temperature throughout the dosing period. Homogeneity and stability of the high- [150 mg/mL] and low- [20 mg/mL] dosing suspensions were assessed in the range-finding study and were not performed in this study. Samples of the low-, mid-, and high-dose levels from each batch were taken on the day of preparation and analyzed for concentrations attained.

RESULTS

The dosing suspensions were found to be homogeneous and stable for ≥20 days at room temperature [range-finding study], and each batch was determined to be within ± 10% of the desired concentration [pages 49 and 382 of the report].

6. Dosage administration: Fluroxypyr MHE was administered via gavage at dose levels of 0 [corn oil], 100, 300, 600 mg/kg/day on gestation days 6 through 15 to 28 presumed pregnant rats/sex/group. The initial dosing volumes were based on day 6 body weights and were adjusted on days 9 and 12 of gestation to changes in individual body weight. The Fluroxypyr acid equivalents were not provided for the dose levels utilized in this study.

C. OBSERVATIONS

1. Maternal observations and evaluations - The dams were checked twice daily for signs of pharmacologic or toxicologic effects and mortality and on days 0, 6-16 and 20 of gestation were given a detailed physical examination [performed ≈1 hour after dosing of all rats]. Body weights were recorded on days 0, 6, 9, 12, 16 and 20 of gestation. Day 20 gestation body weights are presented as actual and corrected [actual day 20 body weight - gravid uterine weight]. Food consumption was measured during gestation intervals 0-6, 6-9, 9-12, 12-16, and 16-20. Surviving dams were sacrificed on day 20 of gestation [exsanguination following anesthesia with CO_2] and subjected to complete gross postmortem

examinations, which included external gross examinations of all surfaces, all orifices, the cranial cavity, carcass, the external surface of the spinal cord and sectioned surfaces of the brain, nasal cavity, and paranasal sinuses, and the thoracic, abdominal and pelvic cavities and their viscera, and the cervical tissues and organs. Liver, kidneys, and gross lesions were saved for all dams. The weight of the liver and kidneys were recorded. **REPRODUCTIVE SYSTEM**: The intact uterus [ovaries attached] was removed from the abdominal cavity, weighed, and the number and location of (1) live fetuses [movement in response to touch], (2) dead fetuses [lack of movement in response to touch but no evidence of tissue degeneration], (3) late resorptions [recognizable dead fetus undergoing degeneration regardless of size], (4) early resorption [evidence of implantation but no recognizable fetus, (5) implantation sites were recorded for each uterine horn. The ovaries were dissected free from the uterus and evaluated for the presence and number of corpora lutea. When no uterine implants were apparent grossly, the uterus was stained with ammonium sulfide [method of Salewski]. When no foci were visualized poststaining, the female was considered not pregnant.

2. Fetal Evaluations - Each fetus was individually identified, weighed, sexed externally [ano-genital distance] and given a gross examination for external malformations/variations to include observation for palatal defects. **Visceral Evaluations**: Approximately half of the fetuses in each litter [alternating fetuses within the litter] were evaluated [performed on the fresh fetal specimens shortly after removal from the uterus] for visceral malformations/variations using a microdissection procedure [modified Staples]. These fetuses were decapitated, and the head was fixed in Bouin's solution for later evaluation. The fetal specimens were dissected to permit evaluation of the tissues in the thoracic and abdominal cavities and following this were eviscerated [viscera discarded] and placed in individual plastic cassettes and stored in a 70% ethanol solution. Following fixation, the fetal heads were sectioned, and the serial transverse sections were evaluated for malformations of the palate, eyes, and brain under a dissecting microscope. Following evaluation, the head sections were placed in plastic cassettes for storage in ethanol also. **Fetal Skeletal Evaluations**: The remaining fetuses in each litter were killed via an overdose of inhaled CO_2, and the intact fetuses were eviscerated [internally sexed by inspection of the gonads] and processed for staining of the ossified skeletal structures using the Alizarin Red S staining procedure of Crary [modified]. Fetal skeletal specimens were evaluated under a dissecting microscope for ossification variations and malformations. **Late Resorptions**: Late resorptions were weighed, examined grossly for external malformations, and discarded.

D. DATA ANALYSIS

Statistical analyses: dam body weight/gain, corrected body weights and net body-weight change, gravid uterine weight, food consumption, organ weights [absolute and relative], reproduction data: Bartlett's test for equality of variances; based on outcome, a parametric [standard one way ANOVA using F distribution to assess significance; if significant, Dunnett's test used] or nonparametric [Kruskal-Wallis test; if differences were indicated, a summed rank test (Dunn) was used]. incidence of litters with resorption sites, mortality and pregnancy rates, incidence of fetuses with malformations/variations [external, soft tissue, skeletal], incidence of litters containing fetuses with malformations/variations: a standard chi-squared analysis was performed to determine if the proportion of incidences differed between groups; next each treatment group was compared to control using a 2x2 Fisher's Exact Test, followed by the Bonferroni inequality test. Armitage's test for linear trend was performed.

II. **RESULTS**

A. MATERNAL TOXICITY

1. Mortality and Clinical Observations: Deaths occurred at the high-dose level only [Table 1]. Eight dams at the 600 mg/kg/day dose level were found dead on gestation days 10 to 17 following 4 to 10 days of treatment. All but one of these dams were pregnant. Excessive salivation [Table 2] was observed only in treated dams at the 100, 300, and 600 mg/kg/day dose level [7.1%, 28.6%, 78.6% [75% of those found dead], respectively], and this was considered by the author to represent a local response to residual amounts of the test material in the buccal cavity from the dosing procedure and not a direct, systemic effect of treatment, since it also occurred in the range-finding study within several minutes of dosing, was sporadic, and it was not observed at 100 mg/kg/day in the range-finding study. Other clinical signs observed at the high-dose level include staining of the skin/fur in the ano-genital area [18 high-dose dams and 1 mid-dose dam], lethargy [found-dead dams], hypothermia [found-dead dams], labored breathing [found-dead dams], black/brown stains around the mouth [found-dead dams], pale appearance [found-dead dams], and irregular gait [found-dead dams].

Table 1. Mortality of High-Dose Group

Days of gestation	# of Days of Treatment	# of implantations
10	4	16
12	6	15
13	7	12
13	7	18
14	8	14
14	8*	0 [not pregnant]
16	10	16
17	10*	15

* oily substance in lungs suggests dosing errors; data from page 31 of the report

Table 2. Clinical Signs in High-Dose Dams That Died

Sign/day(s) of occurrence/dam #	4571	4577	4582	4586	4590	4592	4596	4598
excessive salivation	-	9,10	13,14	10	9-13	9-15	-	11,12
lethargic	-	-	16	13	-	15	12	-
hypothermia	-	-	16	-	-	15	-	-
labored breathing	-	-	16	13	13	-	12	-
AG stains	-	-	14-16	12,13	-	-	-	-
alopecia	9	-	9-14	-	-	11-15	10-12	-
irregular gait	-	-	-	-	-	-	12	-
day found dead	10	12	17	14	14	16	13	13

data from Appendix G [pages 101-104] of the report

2. Body Weight: Body weight was comparable among the groups throughout the study, and body-weight gains of the control, low-, and mid-dose dams were comparable also. At the high-dose level, body-weight gain was decreased [59%-80% of control] relative to the control during the dosing period [Table 3] and also prior to dosing [94% of control]. Body-weight gain for the high-dose dams during the post-dosing interval was comparable to the control. Corrected body weight was comparable among the control, low-, and mid-dose groups, but the high-dose dams displayed a decreased gain [89% of control]. For the dosing intervals day 6-9, 9-12, 12-16, and 6-16 of gestation, the reduced body-weight gains at the high-dose level are considered treatment-related.

Table 3. Body Weight [% of control]/Gain [g] During Gestation

Time/Dose (mg/kg/day)	0	100	300	600
BODY WEIGHT♦				
0	100	101	101	100
6	100	101	102	99
9	100	101	102	98
12	100	101	103	98
16	100	101	102	96
20	100	100	101	98
BODY-WEIGHT GAIN				
day 0-6	32	33	37	30 [94]♪
day 6-9	5	5	6	4 [80]
day 9-12	14	16	15	10 [71]
day 12-16	29	27	26	17* [59]
day 6-16	48	47	47	37 [77]
day 16-20	64	64	63	66 [103]
day 0-20♦	145	144	147	136 [94]
CORRECTED BODY WEIGHT GAIN [g]	34.8	35.0	32.9 [95]	30.9 [89]

data from pages 68, 73, & 79; ♦ calculated by reviewer using data from page 68 of report; ♪ [% of control]

3. Food Consumption - Food consumption was comparable among the control, 100, and 300 mg/kg/day dose groups throughout the study, although the low-dose dams displayed a lower intake during the day 9-12 interval [94% of control]. A decrease in food consumption was observed at the high-dose level during the day 9-12 [93% of control] and day 12-16 [91% of control] intervals [Table 4]. The lower intake displayed by the high-dose dams is considered a treatment-related effect indicative of maternal toxicity.

Table 4. Food Consumption [% of control]			
Time/Dose (mg/kg/day)	100	300	600
day 0-6	98	101	96
day 6-9	97	101	97
day 9-12	94	99	93
day 12-16	100	101	91
day 16-20	101	100	102

data from page 85 of the report

4. Gross Pathology - There were no treatment-related gross pathology findings in any of the dams at any dose level. The cause of death of the 8 high-dose dams that died on test was not evident. The findings in most of these dams [red discoloration of the lungs and thymus] were stated to be common findings for animals that die and are not exsanguinated prior to postmortem examination. Mean liver and kidney weights [absolute and relative] were comparable among the control and treated groups.

5. Cesarean Section Data - Pregnancy rate was not adversely affected by treatment [Table 5], but due to deaths, there were only 18 dams at the 600 mg/kg/day level. There were no abortions or premature deliveries, and with the exception of one mid-dose dam who displayed 25 corpora lutea and only one implantation site, which was a late resorption, no litters were totally resorbed. All dams that survived had live fetuses at necropsy, and there were comparable numbers of corpora lutea, implantations, and live fetuses per litter. There were no dead fetuses. There was no increase in the number of resorptions at any dose level, and only the low- and mid-dose groups had late resorptions [1 at each dose level].

Table 5: Cesarean Section Observations

GROUP:	0 mg/kg/day	100 mg/kg/day	300 mg/kg/day	600 mg/kg/day
# Females mated	28	28	28	28
# Pregnant Females	25	28	27	25
Pregnancy Rate (%)	89.3	100	96.4	89.3
Maternal Wastage				
#Died	0	0	0	8
#Died/pregnant	0	0	0	7
#Died/Non pregnant	0	0	0	1
#Aborted	0	0	0	0
#Premature Delivery	0	0	0	0
# Females with 100% intrauterine deaths	0	0	1♪	0
# Females with live fetuses at necropsy (%)	25 (100)	28 (100)	26 (96.3)	18 (100)
Total # Corpora Lutea	394	455	430	286
Corpora Lutea/dam	15.8	16.3	15.9	15.9
Total # Implantations	372	417	388	268
Implantations/Dam	14.9	14.9	14.4	14.9
Total # Live Fetuses	355	394	376	254
Live Fetuses/Dam	14.2	14.1	13.9	14.1
% of implantations♣	95.4	94.5	96.9	94.8
Total # Resorptions	17	23	12	14
Early	17	22	11	14
Late	0	1	1	0
Resorptions/Dam	0.68	0.82	0.44	0.77
# Litters w/resorptions (%)	12(48)	17(60.7)	10(37)	9(50)
% Implantations resorbed	4.5	5.7	6.6	5.0
Resorptions/litters w/resorpt.♣	1.4	1.35	1.2	1.56
Resorptions/Implants Ratio				
Total # Dead Fetuses	0	0	0	0
Preimplantation Loss	0.055	0.077	0.076	0.054
Postimplantation Loss (%)♣	4.51	5.71	6.55♪	4.97
Litter Weight (gm)	-	-	-	-
Mean Fetal Weight [gm]	3.41	3.35	3.42	3.32
Mean Male Weight [gm]	3.52	3.46	3.51	3.40
Mean Female Weight [gm]	3.31	3.26	3.34	3.24
Sex Ratio (% Male)♣	0.92 (47.9)	0.96 (49.0)	1.0 (50.0)	1.15 (53.5)
Mean # Males♣	6.8	6.9	6.96	7.6
Mean # Females♣	7.4	7.2	6.96	6.6
Gravid Uterus (gm)[% of control]	77.6	76.3	77.6	75.0 [96.6]♦
Mean Weight of Placentas (gm)	-	-	-	-
Corrected Dam Body Weight (gm)	289.2	292.2	293.2	283.2
Corrected Dam Weight Change (gm)	34.8	35.0	32.9	30.9 [89]

data from pages 79 [Appendix E] and 105-109 [Appendix H] of the report; ♪ one dam had 25 corpora lutea, one implant, which was a late resorption [if this dam is excluded, postimplantation loss is 2.95%]; ♣ calculated by reviewer; ♦ [% of control]; - not provided;

9

B. DEVELOPMENTAL TOXICITY

1. External Examination - Fetal body weight [Table 6] was comparable among the groups for both sexes, and there was no adverse effect on the sex ratio at any dose level. There was no increase in the incidence of external malformations [# of fetuses with and # of litters with fetuses with] with increasing dose of Fluroxypyr methylheptyl ester [Table 7]. A control fetus had a filamentous tail [in 2 fetuses out of 7308 fetuses in the historical control] and another control fetus from a different litter had an umbilical hernia [not listed in historical control data]. A mid-dose fetus had a cleft palate [in 1 fetus out of 7308 fetuses in the historical control], and a high-dose fetus had a protrusion of viscera through an opening in the abdominal wall [omphalocele; not listed in historical control data]]. There was no discussion regarding external variations.

Table 6. Fetal Body Weight [grams]

Dose/Sex	0 mg/kg	100 mg/kg	300 mg/kg	600 mg/kg
males♪	3.52	3.46	3.51	3.40
females	3.31	3.26	3.34	3.24
♪ combined	3.41	3.35	3.42	3.32

data from page 105 of the report

Table 7. Fetal/Litter External Malformations

Dose/Incidence	0 mg/kg	100 mg/kg	300 mg/kg	600 mg/kg
fetal incidence				
#/# examined	2/355	0/394	1/376	1/254
%	0.6	0	0.3	0.4
litter incidence				
#/# examined	2/25	0/28	1/26	1/18
%	8.0	0	3.8	5.6

data from page 247 [Appendix L-1] of the report

2. Visceral Examination - **MALFORMATIONS** The incidences of fetuses with visceral malformations and litters with fetuses with visceral malformations was comparable among the groups. There were no visceral malformations observed at the high-dose level. The control, low-, and mid-dose groups each had one fetus from one litter with a visceral malformation. The control fetus displayed microphthalmia [2 fetuses in 2 litters of the historical control (HC) of 3794 fetuses and 514 litters], the low-dose fetus displayed a folded retina [in 5 fetuses in 3 litters of historical control], and the mid-dose fetus displayed a malformation that involved the abnormal course of the ascending portion of the aortic arch, the latter passing dorsal instead of ventral to the tracheal/esophageal trunk [retroesophageal; not listed in HC]. **VARIATIONS** The incidence of visceral variations was comparable among the groups, both on a fetal and litter basis [Table 8]. Tortuous ureter [87

fetuses out of 3794 fetuses/65 litters out of 514 litters in HC] was displayed in 3 high-dose fetuses in 2 litters, in 2 control fetuses in 2 litters, in 5 low-dose fetuses in 3 litters, and in 1 mid-dose fetus in 1 litter. Distended renal pelvis [in 6 fetuses in 4 litters of HC; one study had 3 fetuses of 156 fetuses in 2 of 23 litters] was observed in one control and one low-dose fetuses, and in one low-dose fetus there was the absence of an innominate artery [3 fetuses/3 litters of the HC].

Table 8. Fetal/Litter Visceral Variations

Dose/Incidence	0 mg/kg	100 mg/kg	300 mg/kg	600 mg/kg
fetal incidence #/# examined %	2/185 1.1	7/200 3.5	1/195 0.5	3/132 2.3
litter incidence #/# examined %	2/25 8.0	5/28 17.9	1/26 3.8	2/18 11.1

data from page 284 [Appendix M-2] of the report

3. Skeletal Examination - **MALFORMATIONS** Skeletal malformations were observed only in the control [one fetus] and high-dose groups [2 fetuses in 2 litters]. The control fetus with the filamentous tail displayed an absence of sacral and caudal vertebrae. Wavy ribs was observed in one high-does fetus [observed in 23 out of 3519 fetuses of the historical control and in 16 of 513 litters; highest 7 fetuses in 168 fetuses], and angulated bones of the forelimbs [bent radius, bent ulna(ae), and bent scapula(ae)] were noted in another high-dose fetus [not reported in HC]. **VARIATIONS** Although the overall incidences of fetuses and litters with fetuses with one or more ossification variations were comparable among the groups [Table 9], there was an increase compared to the concurrent control in the incidence of two ossification variations [**incompletely ossified cervical vertebral transverse processes and incompletely ossified pubes**] at the high-dose level, which are considered suggestive of a retardation of ossification [Table 10]. The incidence [on both a fetal and litter basis] of both variations at the high-dose level is outside the historical control data. However, the litter incidence of incompletely ossified cervical vertebral transverse processes is also elevated at the mid-dose level and is greater than that observed in the high dose pups. The biological significance of the increase is not known.

Table 9. Fetal/Litter Skeletal [Ossification] Variations

Dose/Incidence	0 mg/kg	100 mg/kg	300 mg/kg	600 mg/kg
fetal incidence #/# examined %	120/172 69.8	136/194 70.1	142/181 78.5	96/123 78.0
litter incidence #/# examined %	25/25 100	28/28 100	26/26 100	18/18 100

data from page 312 [Appendix N-7] of the report

Table 10. Fetal/Litter Skeletal [Ossification] Variations

Variation/Incidence/Dose	0 mg/kg	100 mg/kg	300 mg/kg	600 mg/kg
# fetuses examined	172	194	181	123
# litters examined	25	28	26	18
pubis(es)-incompletely ossified				
fetal	4[2.3]♦	4[2.1]	7[3.9]	11[8.9]
litter	4[16.0]	3[10.7]	6[23.1]	5[27.8]
recent historical control data				
fetal {mean(%)/range(%)}				2.8{0.6-6.0}
litter {mean(%)/range(%)}				13.8{4.2-26.1}
cervical transverse process(es) incompletely ossified				
fetal	11[6.4]	8[4.1]	19[10.5]	17[13.8]
litter	6[24.0]	5[17.9]	13[50.0]	8[44.4]
recent historical control data				
fetal {mean(%)/range(%)}				4.3{1.2-10.9}
litter {mean(%)/range(%)}				19.4{4.5-44.0}
pubis(es)-not ossified				
fetal	0	1[0.5]	3[1.7]	1[0.8]
litter	0	1[3.6]	3[11.5]	1[5.6]
Presence of cervical ossification				
fetal	2[1.2]	3[1.5]	1[0.6]	0
litter	1[4.0]	3[10.7]	1[3.8]	0
hyoid-not ossified				
fetal	33[19.2]	23[11.9]	44[24.3]	42[34.1]
litter	16[64.0]	11[39.3]	15[57.7]	12[66.7]
recent historical control data				
fetal {mean(%)/range(%)}				19.8{9.2-33.9}
litter {mean(%)/range(%)}				56.9{33.3-77.3}
hyoid-incompletely ossified				
fetal	3[1.7]	2[1.0]	10[5.5]	3[2.4]
litter	2[8.0]	2[7.1]	8[30.8]	3[16.7]
malar(s)-incompletely ossified				
fetal	5[2.9]	6[3.1]	16[8.8]	13[10.6]
litter	4[16.0]	3[10.7]	9[34.6]	5[27.8]
recent historical control data				
fetal {mean(%)/range(%)}				4.3{0.7-10.3}
litter {mean(%)/range(%)}				18.1{4.3-36.7}
parietal(s)-incompletely ossified				
fetal	4[2.3]	3[1.5]	6[3.3]	11[8.9]
litter	4[16.0]	3[10.7]	6[23.1]	5[27.8]
recent historical control data				
fetal {mean(%)/range(%)}				3.7{0.0-11.0}
litter {mean(%)/range(%)}				16.1{0.0-47.8
maxilla(s)-incompletely ossified				
fetal	7[4.1]	4[2.1]	12[6.6]	12[9.8]
litter	5[20.0]	4[14.3]	7[26.9]	4[22.2]
recent historical control data				
fetal {mean(%)/range(%)}				1.8{0.0-4.7}
litter {mean(%)/range(%)}				8.7{0.0-21.7}
presphenoid-incompletely ossified				
fetal	4[2.3]	2[1.0]	2[1.1]	8[6.5]
litter	3[12.0]	2[7.1]	2[7.7]	3[16.7]
presphenoid-not ossified				
fetal	1[0.6]	1[0.5]	0	0
litter	1[4.0]	1[3.6]	0	0

12

Table 10. Fetal/Litter Skeletal [Ossification] Variations

Variation/Incidence/Dose	0 mg/kg	100 mg/kg	300 mg/kg	600 mg/kg
# fetuses examined # litters examined	172 25	194 28	181 26	123 18
thoracic centrum(a)-incompletely ossified fetal litter	 11[6.4] 8[32.0]	 22[11.3] 16[57.1]	 19[10.5] 13[50.0]	 19[15.4] 12[66.7]
thoracic centrum(a)-split fetal litter recent historical control data fetal {mean(%)/range(%)} litter {mean(%)/range(%)}	 0 0	 3[1.5] 2[7.1]	 3[1.7] 3[11.5]	 3[2.4] 3[16.7] 1.0{0.0-3.4} 6.3{0.0-21.7}
sacral transverse process(es)-not ossified fetal litter	 4[2.3] 4[14.0]	 5[2.6] 5[17.9]	 10[5.5] 9[34.6]	 9[7.3] 5[27.8]
lumbar transverse process(es)-incompletely ossified fetal litter	 0 0	 0 0	 1[0.6] 1[3.8]	 1[0.8] 1[5.6]
4th Sternebra-incompletely ossified fetal litter recent historical control data fetal {mean(%)/range(%)} litter {mean(%)/range(%)}	 13[7.6] 9[36.0]	 11[5.7] 8[28.6]	 9[5.0] 6[23.1]	 13[10.6] 10[55.6] 5.5{0.0-21.6} 23.4{0.0-70.0}
4th Sternebra-not ossified fetal litter recent historical control data fetal {mean(%)/range(%)} litter {mean(%)/range(%)}	 0 0	 1[0.5] 1[3.6]	 0 0	 2[1.6] 2[11.1] 0.4{0.0-1.4} 2.4{0.0-9.1}
ribs-1st lumbar rudimentary fetal litter	 0 0	 1[0.5] 1[3.6]	 1[0.6] 1[3.8]	 2[1.6] 1[5.6]
metacarpal(s)-incompletely ossified fetal litter	 4[2.3] 4[16.0]	 1[0.5] 1[3.6]	 3[1.7] 2[7.7]	 6[4.9] 1[5.6]
metacarpal(s)-not ossified fetal litter	 0 0	 1[0.5] 1[3.6]	 1[0.6] 1[3.8]	 1[0.8] 1[5.6]
OVERALL INCIDENCE OF FETUSES W/ VARIATIONS recent historical control data # fetuses with/# examined {%} range (%)	120/172[69.8]	136/194[70.1]	142/181[78.5]	96/123[78.0] 2801/3519{79.4} (60.8-93.8)

data from pages 307-312 [Appendix N] of the report; [%] {%}

III. DISCUSSION

Eight dams at the high dose [600 mg/kg/day] died on test. All dams in the other groups survived until study termination. Clinical signs observed included staining of the skin/fur in the ano-genital area in one mid-dose dam [3.6%] and in 18 high-dose dams [64.3%] and excessive salivation [0%, 7.1%, 28,6%, and 78.6% at the control, low-, mid-, and high-dose levels]. Additionally, in those dams that died, lethargy, hypothermia, labored breathing, irregular gait, and pale appearance were

13

observed. Body weight and food consumption were comparable to the control values at the 100 and 300 mg/kg/day dose levels throughout the study, and there was no apparent treatment-related affect on body-weight gain at these 2 dose levels. At the 600 mg/kg/day dose level, body weight was comparable to the control, but body-weight gain was decreased during the dosing period [59-80% of control] and overall [94% of control]. Corrected body-weight change of the high-dose dams was 89% of the control value. Food consumption was decreased during the dosing period at the high-dose level also. There were no treatment-related gross pathology findings, and liver and kidney weights were comparable among the groups at study termination. There were no abortions or premature deliveries at any dose level. With the exception of one mid-dose dam, there were no dams with 100% intrauterine deaths. All surviving dams had live fetuses at necropsy, and there were comparable numbers of corpora lutea, implantations, resorptions, and live fetuses per dam among the groups. Pre- and postimplantation losses were comparable among the groups. The sex ratio and fetal body weights were comparable among the groups. There was no increase in the incidence of any external malformation, visceral malformation or variation, or skeletal malformation at any dose level. Although the overall incidence of ossification variations was comparable among the groups, there was an increase in the incidence of two ossification variations [incompletely ossified cervical vertebral transverse processes and incompletely ossified pubes] at the high-dose level. An increase in the incidence of incompletely ossified cervical vertebral transverse processes was also noted at the mid-dose level, but there was no dose response. Fluroxypyr methylheptyl ester was toxic to the maternal rats at a dose level of 600 mg/kg/day, as evidenced by the death of 8 of the 28 high-dose dams.

C. STUDY DEFICIENCIES: None that would impact negatively on the interpretation of the study results.

14

Sign-off date: 09/29/97
DP Barcode: d232550
HED DOC Number: 012328
Toxicology Branch: tb2

Sign-off date: 09/29/97
DP Barcode: d232217
HED DOC Number: 012328
Toxicology Branch: tb2